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THE JOHN CRERAR

SYNTHETIC ORGANIC CHEMICALS

PUBLISHED BY

Eastman Kodak Company, Rochester, N. Y.

VOLUME 15 • 1943 • NUMBER 2

A Survey of Preparative Methods for Aromatic Aldehydes

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ALL ALDEHYDE SYNTHESSES in the aromatic series can be divided conveniently into two groups: (1) methods by which the aldehyde group is introduced directly into an active position in the aromatic nucleus, and (2) indirect methods by which a group already present or one which can be introduced into the desired position is modified.

Since the direct methods fail when *meta*-directing groups are present, they can be applied only to hydrocarbons and to compounds containing groups with *ortho-para* directive influence. Of the three direct methods, the Gattermann and *N*-methylformanilide syntheses give the best yields and are to be preferred to that of Reimer and Tiemann.

The indirect methods often afford yields approaching those given by the direct syntheses and have the advantage of making available aldehydes in which the functional group is located in positions other than those accessible by direct substitution. The Sonn-Müller, Stephen, and Rosenmund methods of reducing acid (or nitrile) substituents are the more useful, whereas the methods typified by the halogenation and hydrolysis of toluene, the oxidation of toluene, and the oxidation of benzyl alcohol are

usually applicable only in specific cases. In the more highly substituted molecules encountered in organic synthesis, the methyl or hydroxymethyl groups necessary for the latter types of reactions are generally absent, and their introduction would involve intermediates from which the aldehyde could be prepared by other methods.

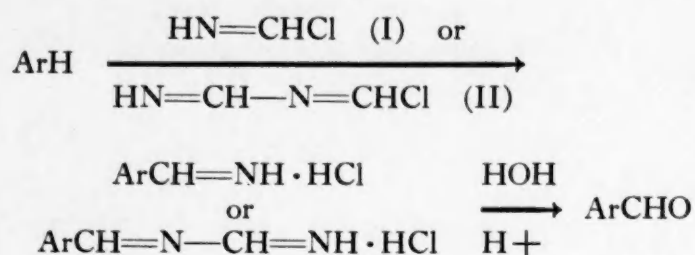
Direct Methods

Gattermann's original method, in which carbon monoxide and hydrogen chloride were allowed to react with an aromatic hydrocarbon in the presence of aluminum chloride, was quite successful, but its failure in the case of phenols and phenol ethers led to the substitution of hydrogen cyanide for carbon monoxide. This modified procedure, which has found extensive use, is usually employed with ether or benzene as a solvent in the presence of zinc chloride or aluminum chloride as a catalyst and at temperatures ranging from 25° for phenolic compounds to 100° for hydrocarbons (1, 2).

With *meta*-dihydroxy compounds no catalyst is necessary; the imino formyl chloride (I) in equilibrium with hydrogen cyanide and hydrogen chloride reacts readily with resorcinol in ether solution, forming the insoluble aldimine hydrochloride which is easily hydrolyzed to

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the aldehyde. Other phenols and phenol



ethers necessitate the use of a catalyst such as zinc chloride or aluminum chloride; the former is more desirable since it has less tendency to cause the cleavage of phenol ethers. In reactions in the presence of a catalyst, the intermediate is chloromethyleneformamidine (II), a double compound consisting of two moles of hydrogen cyanide and one of hydrogen chloride (2).

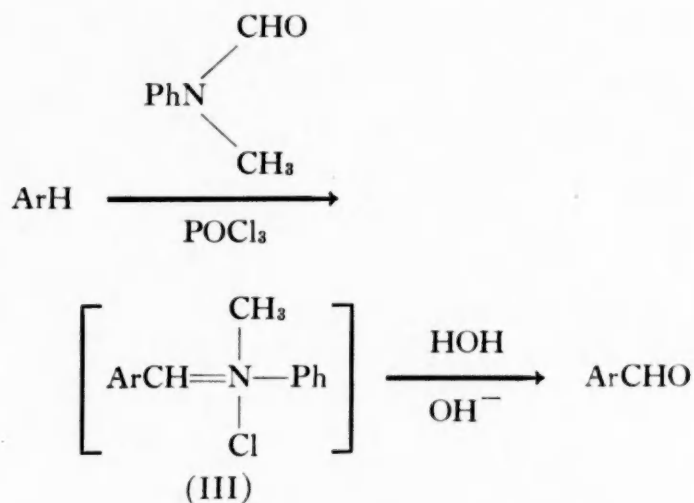
The application of this method to hydrocarbons afforded Hinkel and co-workers good yields of the corresponding aldehydes only under forcing conditions. The temperature was raised to about 80°, excess aluminum chloride was used as a catalyst, and solvents of high chlorine content such as tetrachloroethane and *o*-dichlorobenzene were employed. Chloromethyleneformamidine was the intermediate in this case also, high temperatures being necessary to liberate it from its aluminum chloride complex (in the absence of ethers) and to increase the speed of its combination with hydrocarbons.

In order to avoid handling liquid hydrogen cyanide, Adams replaced it by zinc cyanide (3); thus both hydrogen cyanide and zinc chloride were generated in the reaction mixture. Generally this modification does not affect the yields adversely, but the use of other cyanides as a source of hydrogen cyanide has not been very satisfactory. In some cases, the addition of small amounts of potassium chloride exerts a catalytic effect.

The production of aldehydes by the action of *N*-methylformanilide or formanilide in the presence of phosphorous oxychloride has been known for some time, but only recently has the method

found extensive application. The patent literature lists numerous examples of its use in introducing nuclear aldehyde groups into phenol ethers and tertiary amines. Aromatic hydrocarbons containing particularly reactive positions such as anthracene, pyrene, acenaphthene, and 1,2-benzanthracene have afforded aldehydes in yields in excess of 70 per cent (4).

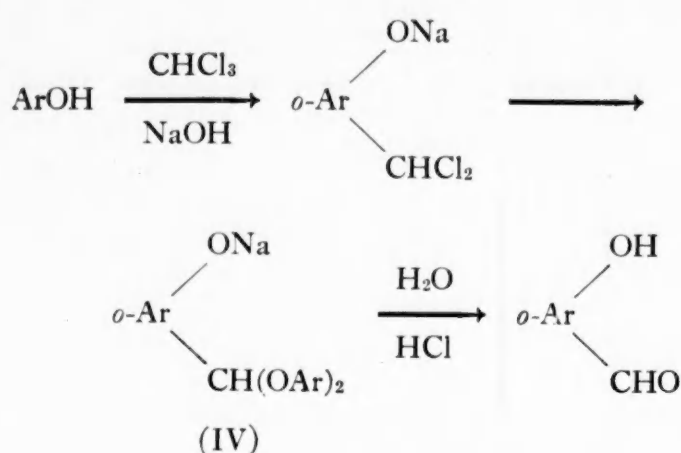
The reaction is usually carried out by mixing the reagents and allowing them to stand at room temperature or by heating them at 100°. Often the addition of a solvent such as ether, benzene, or *o*-dichlorobenzene is necessary in order to effect solution of the aromatic compound. The mixture, which probably contains (III) as the intermediate, is hydrolyzed by means of sodium acetate or



alkali, and the aldehyde is isolated by an appropriate procedure.

The Reimer-Tiemann reaction has the advantage of making available certain *ortho*-hydroxyaldehydes which cannot be prepared conveniently by other methods. It is carried out by adding chloroform to a refluxing alkaline solution of the corresponding phenol. After acidification the reaction mixture is steam-distilled and the aldehyde isolated from the distillate (5).

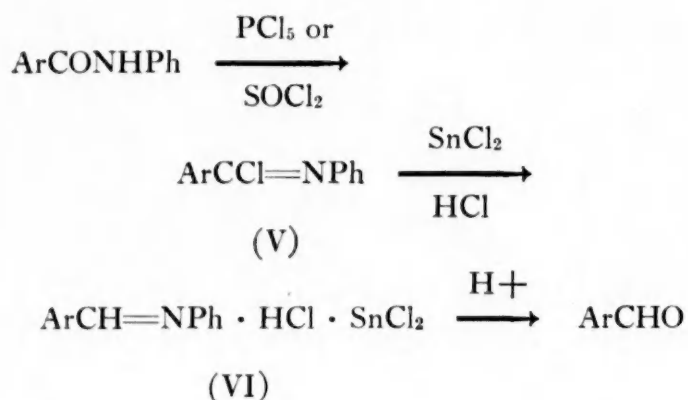
Because of undesirable side reactions of which the most important is the reaction between the intermediate salt of *o*-dichloromethylphenol and unchanged sodium phenylate to form compounds of



the type (IV), yields greater than 35 per cent are rarely obtained. This limitation is a serious disadvantage from the preparative point of view.

Indirect Methods

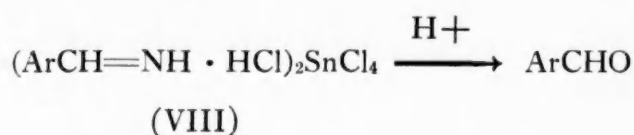
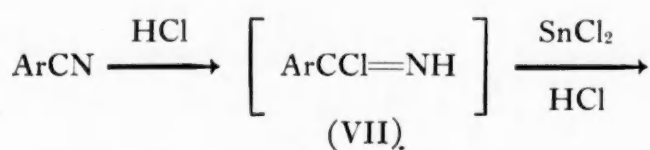
The introduction by Sonn and Müller of stannous chloride for the reduction of imide chlorides provided an excellent indirect method for preparing aldehydes from aromatic acids. The imide chloride (V) is usually prepared by the action of phosphorus pentachloride or thionyl chloride on the anilide, after which the crude chloride is added to an anhydrous solution of stannous chloride in ether saturated with hydrogen chloride. The double salt (VI) which precipitates is hydrolyzed directly to the aldehyde. This reaction is somewhat subject to



hindrance, but even so the yields are rarely less than 50 per cent (6).

The Stephen procedure resembles the above method closely in that it is a reduction of an imide chloride (VII) by stannous chloride. A nitrile is added to the ethereal solution of stannous chloride and the precipitated double salt (VIII) is hydrolyzed by dilute acid. The reac-

tion is not as general as Stephen at first claimed, and it is much more subject to hindrance than the Sonn-Müller method (7). This method has found recent application in the synthesis of compounds related to thyronine.



The basis for the success of the Rosenmund method is the highly selective reducing action of hydrogen on acid chlorides in the presence of palladium precipitated on barium sulfate. Ordinarily, the catalyst is "poisoned" by adding a sulfur-quinoline preparation to prevent the reduction of the aldehyde formed, but numerous reductions have been effected in which no poison seemed necessary. To obtain the best results, it is generally necessary to purify the acid chloride carefully. The reduction is usually carried out in boiling xylene, and the course of the reduction is followed by titrating the hydrogen chloride liberated. Substitution and hindrance have little effect on the reduction, and the conditions are mild enough so that nitro groups are not reduced (8).

Since aromatic acids are readily available by general preparative methods, the Sonn-Müller and Rosenmund methods are particularly valuable. The yields from the two procedures are comparable, and except in isolated instances either method can be used.

Reactions with Grignard Reagents

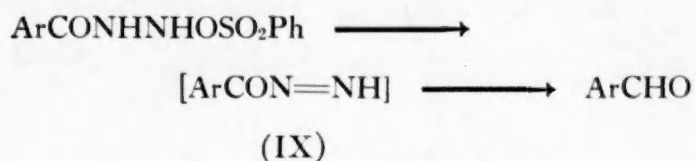
Of the numerous aldehyde syntheses in the literature involving reactions with Grignard reagents, only four have been used with much success in the aromatic series. These involve treatment of the Grignard reagent with one of the follow-

ing reagents, followed by hydrolysis: (1) ethoxymethylene aniline ($\text{PhN}=\text{CHOC}_2\text{H}_5$), (2) ethyl orthoformate, (3) disubstituted formamides (e.g., N-methylformanilide), and (4) carbon disulfide. In the last method the dithio acid obtained is treated with semicarbazide, with formation of the semicarbazone of the corresponding aldehyde, which is hydrolyzed to the aldehyde.

Smith (9) found the first of these to be the most reliable method, but it has the disadvantage that ethoxymethylene aniline is difficult to prepare and is expensive. The next two are quite successful in certain cases and are generally superior to the last method, which gives rise to undesirable side reactions and is subject to hindrance.

A reaction which employs the relatively easily prepared chloromethyl compounds is that introduced by Sommelet in which the chloromethyl compounds are boiled with hexamethylenetetramine in alcoholic solution. The aldehyde is produced directly and often crystallizes from the solution. The application of this method is limited by the availability of the chloromethyl compound, and by the fact that it may fail in extremely hindered cases.

The most recent method involves the decomposition of arylsulfonacylhydrazides by alkali carbonates in ethylene glycol or glycerol solutions at $160-200^\circ$. The decomposition presumably takes place via the intermediate benzoyl diimine (IX) which loses nitrogen (10).



The use of this procedure in syntheses in the thyronine series indicates its preparative value, although other methods starting from aromatic acids are more desirable where they are successful.

References

- (1) Ann. 347, 347 (1906); 357, 313 (1907).
- (2) J. Chem. Soc. 339 (1936) and preceding papers.
- (3) J. Am. Chem. Soc. 45, 2373 (1923).
- (4) See J. Am. Chem. Soc. 64, 1666 (1942) for references.
- (5) Org. Syn. 22, 63 (1942).
- (6) Ber. 52, 1927 (1919).
- (7) J. Am. Chem. Soc., 61, 2248 (1939).
- (8) Ber. 51, 585 (1918).
- (9) J. Org. Chem. 6, 437, 489 (1941).
- (10) See J. Am. Chem. Soc., 63, 487, 2091 (1941) for references.

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1081	1-Asparagine	10 g. ..	1.55 A
498	Pyruvic Acid	100 g. ..	2.50 C
P 5351	Quinone Dioxime (Pract.) MP 252° dec.	10 g. ..	6.50 A
5404	Tetra-iso-butylene BP $109.5-111^\circ/15$ mm.	100 g. ..	8.00 C
P 5378	α -Phenoxypropionic Acid (Pract.) MP $109.5-114^\circ$	100 g. ..	5.00 C
P 5381	α -Phenoxypropionyl Chloride (Pract.)		
	BP $104.5-106^\circ/14$ mm.	100 g. ..	6.00 C
2787	Quinalizarin	10 g. ..	3.00 A
5314	p-Ethoxychrysoidin Hydrochloride	10 g. ..	1.50 A
T 998	Glycolic Acid (70%) (Techn.)	3 kg. ..	2.10 G
P 3091	Naphthalic Anhydride (Pract.)	100 g. ..	4.00 C